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Uloga rosuvastatina u primarnoj i sekundarnoj prevenciji kardiovaskularnih događaja i utjecaj na suradljivost bolesnika

The Role of Rosuvastatin in Primary and Secondary Prevention of Cardiovascular Events and Influence on Patient Compliance

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SAŽETAK: Kardiovaskularne su bolesti vodeći uzrok smrtnosti u svijetu, a povišene masnoće u krvi jedan su od najvažnijih čimbenika rizika za njihov nastanak. U tome je smislu učinkovito smanjenje lipida bitan napredak u smanjenju pobola i smrtnosti od neželjenih kardiovaskularnih događaja, što dokazuju i mnogobrojne studije. Za smanjenje masnoća vrlo su učinkoviti antilipemici, a među njima statini zauzimaju središnje mjesto. Kao statin „nove generacije" ističe se rosuvastatin. To je sintetski statin koji inhibira enzim 3-hidroksi-3-metilglutaril koenzim A reduktazu te na taj način smanjuje sintezu endogenog kolesterola. Dominantni učinak rosuvastatina jest snizivanje LDL kolesterola i ukupnog kolesterola u krvi te je on jedini statin koji je pokazao pozitivan učinak u povećanju koncentracije HDL kolesterola, i to do 15 %. U literaturi su opisani i protuupalni, antioksidativni i antitrombotski učinci ovoga lijeka, koji dodatno smanjuju rizik od kardiovaskularnog pobola i smrtnosti, a ne mogu se pripisati isključivo smanjivanju razine ukupnog kolesterola. Najčešća nuspojava ovog lijeka jest mijalgija koja je jedan od najvažnijih razloga zašto bolesnici odustaju od statinske terapije i pribjegavaju „alternativnim", često neučinkovitim rješenjima. Kako je liječenje hiperlipidemije od ključne važnosti za smanjenje kardiovaskularnog rizika, potrebno je naglasak staviti na redovito uzimanje lijeka i na nalaženje adekvatnog načina da bolesnik ostane na terapiji statinima. U tome smislu širok raspon jačine rosuvastatina u 6 različitih doza od 5 do 40 mg omogućuje da količinu lijeka prilagodimo potrebama bolesnika kako bi liječenje bilo učinkovito, a eventualne neželjene nuspojave lijeka svedene na minimum.

SUMMARY: Cardiovascular diseases are the leading cause of death in the world with hyperlipidemia being one of the most important risk factors in their development. Therefore, numerous randomized controlled trials conducted, showed decrease morbidity and mortality from adverse cardiovascular events by effective lipid reduction. Statins are the most effective medications used in treatment of hyperlipidemia. Rosuvastatin represents a "new generation" statin. It is a synthetic statin that inhibits the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, and therefore reducing the synthesis of endogenous cholesterol. The major effect of rosuvastatin is the reduction of LDL-cholesterol, and total cholesterol in the blood. It is the only statin that has been shown to increase the levels of HDL-cholesterol up to 15%. The anti-inflammatory, anti-oxidative, and anti-thrombotic effects of the drug were demonstrated in various studies, causing further decrease in cardiovascular morbidity and mortality, that effect is beyond the one described only by the reduction in total cholesterol levels. The most common side-effect of statin treatment is myalgia, causing the non-adherence and discontinuation of the medication, leading to "alternative" drug treatment. However, the approach of alternative drug treatment often showed itself to be ineffective solution. Since treating hyperlipidemia is crucial in reducing cardiovascular risk, the importance of adherence to treatment, and achieving patient compliance to statin therapy must be emphasized. Rosuvastatin is available in 6 different doses from 5 to 40 mg, allowing the physician to adjust the dose of medication according to the patient's needs, to maintain highest treatment effect while reducing unwanted side-effects at the minimum.

KLJUČNE RIJEČI: rosuvastatin, prevencija, kardiovaskularne bolesti.

KEYWORDS: rosuvastatin, prevention, cardiovascular diseases..

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Rosuvastatin kao „super“ statin u primarnoj i sekundarnoj prevenciji kardiovaskularnih događaja

Kardiovaskularne bolesti vodeći su uzrok smrtnosti u svijetu: 42 % ukupne smrtnosti žena i 38 % smrtnosti muškaraca prije 75. godine života u Europi su posljedica kardiovaskularnih bolesti. Stoga je iznimno važno identificirati i utjecati na čimbenike rizika za razvoj ove bolesti, uključujući i hiperlipidemiju jer je prevencija djelotvorna: bilježi se 50 %-tna redukcija smrtnosti od koronarne bolesti srca zbog promjena u ponašanju, što se tiče čimbenika rizika, te 40 %-tna redukcija zbog boljeg liječenja čimbenika rizika. Postoje brojni mitovi povezani sa statinima, od toga da prije nitko nije liječio povišeni kolesterol, a ljudi su živjeli dugo, do toga da se ne isplati liječiti osobe starije od 60 godina, da statinska terapija bolesnicima ne produljuje život, da statine nema potrebe uzimati cijeli život te da oni mogu oštetiti jetru, mišiće i na kraju da statini uzrokuju šećernu bolest. Desetci tisuća pacijenata u kliničkim studijama i stotine milijuna pacijenata na statinskoj terapiji diljem svijeta upućuju nas na to da su statini najučinkovitiji lijekovi za smanjenje kardiovaskularnog morbiditeta i mortaliteta. Osim toga, ako je procjena da će 2020. godine prosječno trajanje života žena biti veća od 80 godina, a muškaraca viša od 75 godina te da se najviše kardiovaskularnih incidenata događa u dobi nakon 60. godine, tada nam postaje jasnija važnost statina u primarnoj i sekundarnoj prevenciji tih bolesti[1-5].

Iako na tržištu postoje različite vrste statina, danas se najčešće propisuju atorvastatin i rosuvastatin zbog svoje učinkovitosti i sigurnosti. Rosuvastatin je sintetski hidrofilni statin koji djeluje tako što inhibira enzim 3-hidroksi-3-metilglutaril koenzim A reduktazu (3-HMG-CoA). Djeluje tako što snizuje vrijednosti LDL kolesterola (LDL-a) i ukupnoga kolesterola, dok jedini od statina povećava u krvi koncentraciju HDL kolesterola (HDL-a). Poluvrijeme eliminacije iznosi mu oko 19 sati te se primjenjuje peroralno jednom na dan, neovisno o uzimanju hrane. Izlučuje se dominantno nepromijenjen bubrezima (2/3), dok se ostatak lijeka izlučuje bilijarnom sekrecijom (koristeći se transportnim proteinima OATP1B1 i BCRP). Stoga je potreban oprez u bolesnika s umjereno oštećenom bubrežnom funkcijom te je u takvih bolesnika potrebno maksimalnu dnevnu dozu rosuvastatina reducirati na 20 mg. Samo se 10 % rosuvastatina metabolizira preko jetre, što ga čini prikladnom terapijom za bolesnike koji uzimaju više lijekova. Dokazano je da rosuvastatin ima nizak potencijal za interakciju s ACE inhibitorima, sartanima, beta-blokatorima, oralnim antidijabeticima, nesteroidnim antireumaticima i antibioticima, a to su ujedno i najčešće propisivani lijekovi u bolesnika s kardiovaskularnim bolestima i u starijih bolesnika. Treba napomenuti da lijekovi koji se koriste transportnim proteinima OATP1B1 i BCRP u jetri (kao što su ciklosporin i određeni antivirusni lijekovi) mogu utjecati na koncentraciju rosuvastatina u krvi te ga je u tim slučajevima potrebno zamijeniti nekom alternativnom terapijom. Rosuvastatin je apsolutno kontraindiciran samo u bolesnika s teško oštećenom bubrežnom funkcijom, u trudnoći i pri dojenju. Miopatija je jedna od najčešćih nuspojava pri liječenju statinima pa je stoga potreban oprez pri uvođenju rosuvastatina u redovitu terapiju bolesnika s predisponirajućim čimbenicima za miopatiju[5].

Rosuvastatin se pokazao kao najpotentniji statin na tržištu u snizivanju vrijednosti LDL-a u plazmi. Njegov učinak na po-

Rosuvastatin as a “super” statin in primary and secondary prevention of cardiovascular events

Cardiovascular diseases (CVD) are the leading cause of death in the world: resulting in 42% of total mortality in women, and 38% in men before the age of 75, in Europe, caused by cardiovascular diseases. Therefore, to prevent development of CVD it is highly important to identify, and modify cardiovascular risk factors. The studies showed a 50% reduction in mortality from coronary heart disease by changes in behavior affecting the CVD risk factors, and a 40% reduction due to improved treatment of CVD risk factors.

There are many myths associated with statin treatment, including the claims: that no-one treated elevated cholesterol before and people lived longer, that there is no point treating persons over the age of 60, as the statin therapy would not extend the lives of patients at that age, that there is no benefit to take statins during lifetime, that they could damage the liver and muscles, and finally that statins could be the cause of diabetes. However, tens of thousands of patients in clinical trials and hundreds of millions of patients receiving statin therapy all over the world, showed that statins are the most effective drugs in reducing cardiovascular morbidity and mortality. Additionally, as the most cardiovascular events happen in the patients older then 60, taking into account estimation that by the 2020, the average lifespan of women will be above 80 years, and in men above 75 years, the importance of statins in primary and secondary prevention of CVD becomes even clearer[1-5].

Although different types of statins are currently available on the market, due to their effectiveness and safety, atorvastatin and rosuvastatin are the ones most commonly prescribed.

Rosuvastatin is a synthetic hydrophilic statin that works by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (3-HMG-CoA). It reduces LDL-cholesterol (LDL) and total cholesterol values, while being the only statin that also increases HDL-cholesterol (HDL). Its elimination half-life is 19 hours, and it is taken orally once a day irrespective of food intake. Two third of rosuvastatin is excreted dominantly unchanged via the kidneys, while the rest of the drug is excreted through biliary system (using the transport proteins OATP1B1 and BCRP). Therefore, care must be taken in patients with moderately impaired renal function, and the maximum daily dose of rosuvastatin in kidney impairment must be limited to 20 mg. Only 10% of rosuvastatin is metabolized through the liver, making it an appropriate choice of treatment for patients on multiple medications. It has been demonstrated that rosuvastatin has a low potential for interaction with ACE inhibitors, sartans, beta-blockers, oral antidiabetics, nonsteroidal antirheumatics, and antibiotics, which are the drugs most commonly prescribed in older patients, and patients with CVD. It should be noted that medications that use the transport proteins OATP1B1 and BCRP in the liver (such as cyclosporine and certain antiviral drugs) can influence the concentration of rosuvastatin in the blood, in which circumstances alternative treatment should be considered. Severe renal impairment, pregnancy, and breastfeeding are the only absolute contraindications for Rosuvastatin treatment. Myopathy is one of the most common side-effect dur-

višenje HDL-a omogućuje mu najveći utjecaj od svih statina na aterogeni indeks plazme (log/TG/HDL/). S obzirom na to da zaobilazi metabolizam jetrenih enzima, vjerojatnost pojavljivanja nuspojava manja je nego uz primjenu lipofilnih statina kao što je atorvastatin. To je posebno bitno u starijih bolesnika koji u svojoj redovitoj terapiji uporabljuju i po nekoliko vrsta lijekova. Naposljetku, dijabetičari su posebna skupina bolesnika u kojih je rosuvastatin superioran nad ostalim statinima zbog svoje potentnosti[6].

Ne treba zaboraviti ni na dodatne pleotropne učinke rosuvastatina koji se očituju u dodatnom smanjenju kardiovaskularnog rizika bez obzira na snizivanje razine kolesterola. Ti su učinci primarno vezani za antiinflamatorno djelovanje, poboljšanje endotelne funkcije i stabilizacije aterosklerotskoga plaka, što uzrokuje regresiju plaka i smanjuje progresiju ateroskleroze[3]. Zbog tog učinka rosuvastatin pokazuje učinkovitost u prevenciji velikih kardiovaskularnih događaja u žena starijih od 60 godina i muškaraca starijih od 50 godina koji su imali uredne vrijednosti LDL-a, a visoke vrijednosti upalnih parametara (hs-CRP)[7].

Rosuvastatin se rabi kao tablete u 6 različitih doza: 5, 10, 15, 20, 30 i 40 mg, što omogućuje adekvatno titriranje doze lijeka i postizanje adekvatnoga snizivanja vrijednosti LDL-a prema smjernicama Europskoga kardiološkog društva i Europskoga društva za aterosklerozu. Podatci iz kliničke prakse pokazuju da liječnici obično ne propisuju najviše jačine statina te da većina bolesnika prima jednu od dviju najnižih doza. Obično se liječnici ne usuđuju dvostruko povećati postojeću dozu statina pa stoga dolazi do potrebe za statinima srednje jačine. Širok raspon jačina rosuvastatina omogućuje prilagodbu liječenja prema potrebama pojedinih pacijenata te povećava vjerojatnost postizanja ciljne razine lipida[8].

Danas se rosuvastatin pokazao dominantnim, posebno u dijabetičara zbog svoje potentnosti u snizivanju LDL kolesterola, ali i zato što povoljno djeluje na cjelokupni lipidni profil. Liječnici se odlučuju za rosuvastatin kada su vrijednosti lipida u krvi izrazito visoke, kada je kardiovaskularni rizik u bolesnika izrazito velik i kada, koristeći se drugim statinima, ne uspiju postići ciljne vrijednosti lipida u krvi.

Zaključak

Rosuvastatin je antilipemik koji svojim mnogobrojnim potentnim djelovanjima omogućuje adekvatno snizivanje ukupnoga i LDL kolesterola te povišenje HDL-a, čime se postiže poželjan lipidni profil. Primjenjuje se u primarnoj i sekundarnoj prevenciji kardiovaskularnih događaja, napose u dijabetičara, te je pokazao učinkovitost i u bolesnika u kojih drugi statini nisu pokazali adekvatan učinak.

Dosadašnje nam spoznaje govore da su statini provjerena terapija više od 25 godina. Ne samo da učinkovito snizuju razinu lipida u krvi nego imaju i niz drugih povoljnih djelovanja, čime smanjuju kardiovaskularni rizik i produljuju život bolesnika[8]. Statini su i sigurna terapija jer imaju vrlo malo nuspojava te ih stoga treba uzimati, kada je indicirano, do kraja života.

Nažalost, danas se često, zbog neadekvatne edukacije i liječnika i bolesnika, njihove međusobne (ne)komunikacije i posljedične nesuradljivosti, odustaje od uzimanja lijeka, a, ako se on i uzima, nerijetko su doze statina neadekvatne.

ing statin treatment, therefore, rosuvastatin should be avoided or used cautiously in patients with known predisposition to myopathy[5].

Rosuvastatin is shown to be the most effective statin on the market in reducing LDL values in blood, that also effectively increases HDL, therefore the beneficial effect on atherogenic index of plasma (log(TG/HDL)) of all statins is the strongest with the use of rosuvastatin. Given that it bypasses the liver enzyme metabolism, the likelihood of side-effects is lower than with the use of lipophilic statins such as atorvastatin. This is highly important in older patients that are on treatment with multiple medications. Finally, diabetics are a subgroup of patients in which rosuvastatin is shown to be more effective in comparison to other statins[6].

Rosuvastatin is also showing additional pleotropic effects, further reducing cardiovascular risk regardless of the decrease in cholesterol levels. These effects are primarily attributed to its anti-inflammatory effects, improved endothelial function, and the stabilization of atherosclerotic plaque, which leads to plaque regression, and slowing the progression of atherosclerosis[3]. Due to this effect, rosuvastatin has been shown effectiveness in the prevention of major cardiovascular events in women above the age of 60 and men above 50 with normal LDL values, and high values of inflammatory markers (hs-CRP)[7].

Rosuvastatin is present at the market as tablets in 6 different doses: 5, 10, 15, 20, 30, and 40 mg, which allows dose titration to achieve appropriate reduction in LDL values according to the guidelines of the European Society of Cardiology, and European Atherosclerosis Society. The wide range of rosuvastatin dosage allows the physician to tailor the treatment to the needs of the individual patient, increasing the likelihood of achieving targeted lipid values[8]. However, data from clinical practice show that the majority of the physicians do not usually prescribe the highest doses of statins. Physicians are generally reluctant to double the existing dose of statins, with most patients receiving one of the two lowest doses.

Now days, rosuvastatin is the most frequently used statin treatment, especially in diabetics due to its potency on lowering LDL cholesterol, but also regarding the overall beneficial effect on the lipid profile. Rosuvastatin is chosen in treatment of patients with especially high lipid values, in patients with very high cardiovascular risk, and patients where other statins failed in achieving targeted lipid levels.

Conclusion

Rosuvastatin is an hypolipemic drug, with numerous effects that cause significant reduction of total and LDL-cholesterol, and increase in HDL, used to achieve the targeted lipid profile. It is effective in primary and secondary prevention of cardiovascular events, especially in diabetics, and its effectiveness has been shown when treatment failure with other statins is present.

Based on the current state of knowledge, statins have been a well-tested therapy of choice for more than 25 years. They not only effectively reduce the level of lipids in the blood, but also have many other beneficial effects, thus reducing cardiovascular risk and extending the patient's lifespan[8]. Statins are also a safe choice of therapy, since they have very few

Stoga kontinuirana edukacija liječnika i bolesnika o učinkovitosti, sigurnosti i potrebi uzimanja statina, s jedne, te mogućnost titriranja rosuvastatina, s druge strane, omogućuje da se postigne najveća moguća korist od liječenja statinima.

side-effects. Therefore when indicated, and should be taken lifelong.

Unfortunately, due to inadequate education of both physicians and patients, and the lack in their communication, with consequent failure in adherence to the treatment, statin therapy is often discontinued, and even when taken regularly, it is often underdosed.

However, continued physicians and patients education on the effectiveness, safety, and necessity of taking statins on the one side, and the possibility of titrating rosuvastatin on the other, will allow achieving targeted lipid values, and consequently enable the highest benefit from statin treatment.

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